

MADOR: A NEW TOOL TO CALCULATE DECREASE OF EFFECTIVE DOSES IN HUMAN AFTER DTPA THERAPY

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Abstract models have been developed to describe dissolution of Pu/Am/Cm after internal contamination by inhalation or wound, chelation of actinides by diethylene triamine penta acetic acid (DTPA) in different retention compartments and excretion of actinide–DTPA complexes. After coupling these models with those currently used for dose calculation, the modelling approach was assessed by fitting human data available in IDEAS database. Good fits were obtained for most studied cases, but further experimental studies are needed to validate some modelling hypotheses as well as the range of parameter values. From these first results, radioprotection tools are being developed: MANagement of DOse Reduction after DTPA therapy.

INTRODUCTION

Since several decades, diethylene triamine penta acetic acid (DTPA) has been used to enhance excretion of Pu/Am/Cm after accidental contamination in human⁽¹⁾. DTPA treatment has to be done promptly after the accident in order to decrease systemic retention associated with the presence of soluble actinides. Depending on chemical forms of the actinides and contamination levels, delayed treatments could also be performed which significantly increase faecal and urinary excretion of the actinides. The first modelling approach has considered that only extracellular actinides are chelated by DTPA and then fastly excreted in urine⁽²⁾. To explain the delay urinary excretion of actinide–DTPA, about 5 % of the chelates are supposed to be retained in an unidentified extracellular compartment with half-time of 1 week. This modelling approach can be applied to single treatments, but in the case of repeated, one's actinide decorporation is underestimated⁽³⁾. Thus, other sources of chelated actinides have to be considered which involved systemic intracellular compartments^(4, 5) and the site of contamination⁽⁵⁾. Recently, identification of the main sources of Pu/Am chelated by DTPA as well as improved knowledge of decorporation processes were obtained from targeted animal experiments. Thus, the structure of new models to describe decorporation of Pu/Am by DTPA have been proposed which take into account actinide speciation and their localisation within different compartments^(6–9). At this time, such complex structures are difficult to be combined with current models used to describe actinide biokinetics in human for dose calculation^(10–13).

Simplification of modelling is needed to provide, in a next future, tools suitable for a radioprotection purpose. The aim of this study was to test a first version of a new radioprotection tool: MANagement of DOse Reduction after DTPA therapy (MADOR) to calculate effective dose reduction associated with DTPA administrations.

MATERIALS AND METHODS

Dissolution model

Figure 1 shows the dissolution model used which is a combination of those reported after inhalation⁽¹⁰⁾ and wound⁽¹³⁾.

Four compound behaviours have been considered corresponding to fractions of deposited material f_b , f_{col} (col as colloids), f_s and f_{ss} . Dissolution rates of these fractions gradually decrease from s_b , s_{col} , s_s and s_{ss} . A fraction f_b of the dissolved actinides is retained in extra- and intracellular pulmonary compartments before reaching the blood stream at a rate s_b . This bound fraction was only considered in alveolar interstitium ($ai1$, $ai2$ and $ai3$) which contains most of the lung actinides for the first years after contamination.

Chelation and excretion models

From recent experimental data^(6–9), it was assumed that once formed actinide–DTPA are stable in the different retention compartments. Ninety per cent of extracellular complexes are promptly excreted in urine and 3 % in faeces. The remainder (~7 %) is retained in cells of soft tissues and return to blood with half-time (λ_{cell}) of about 1 week (Figure 2).

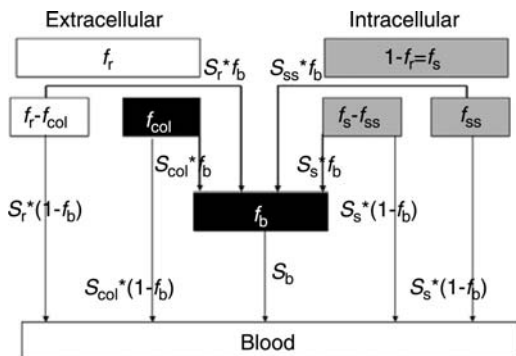


Figure 1. Dissolution model applied to inhalation and wound. Black boxes correspond to compartments in which chelation of actinides by DTPA could occur.

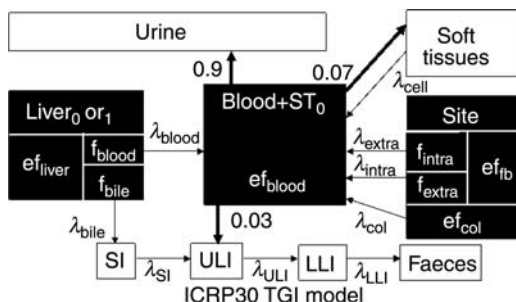


Figure 2. Model applied to describe early chelation. Different fractions of chelated actinides are considered depending on their route of excretion (liver: blood or bile $f_{\text{blood}} + f_{\text{bile}} = 1$) or their location (site: intra- or extracellular $f_{\text{intra}} + f_{\text{extra}} = 1$).

Two chelation processes have been taken into account: early chelation which involves retention compartments at the time of treatment and delayed chelation which involves free intracellular DTPA chelating new actinide deposits.

For simplification, early chelation occurs only in three sites: liver 0 or 1 depending on the systemic model applied, blood and interstitial fluids (ST_0), and at the site of contamination. An efficacy of chelation (ef) is assigned to each of these compartments which corresponds to the fraction of chelated actinides. The rate of transport to blood and to bile (λ), in the case of the liver, varies according to the extra- or intracellular location of the complexes (Figure 2).

Delayed chelation only occurs in the liver and at the contamination site in f_b . Depending on the galenic form and DTPA dosage, a free chelating agent concentration is assigned to these compartments. This concentration decreases at a rate λ_{DTPA} . Above a threshold concentration, chelation efficacy is assigned a constant value, and below, it decreases

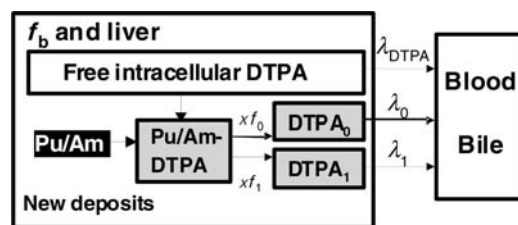


Figure 3. Model applied to describe delayed chelation. λ_{DTPA} corresponds to the rate of transport of free DTPA from cells to blood, whereas two fractions of Act-DTPA are considered ($f_0 + f_1 = 1$) which leave the cells at different rates, λ_0 and λ_1 , respectively. Once transferred, behaviour of Act-DTPA is the same as described in Figure 1.

linearly with an adjustable slope. Two retention compartments of Act-DTPA are then considered with transfer to blood or bile at different rates (Figure 3).

Other models and human data

These three models are coupled to the model of particle transport⁽¹⁰⁾, systemic models of ICRP⁽¹¹⁾, or in the case of Pu, to the model recently proposed by Leggett *et al.*⁽¹²⁾ and gastrointestinal model of ICRP30⁽¹⁴⁾.

The most relevant cases available on the web in IDEAS internal contamination database⁽¹⁵⁾ have been used for a first validation of our simplified modelling approach. A reference number is assigned to each contamination case which corresponds to that provided in the database.

RESULTS AND DISCUSSION

Fit examples

More than 12 inhalation or wound cases involving Pu, Am or Cm could be well fitted using different parameter values. Figures 4 and 5 show the fit examples of well-documented human cases after inhalation exposure to aerosols containing Am or Pu.

Case 17 provides measurements of excretion and retention. Chelation of Am is clearly pointed out in the liver which is associated with an increase in faecal excretion of the actinide similar to that measured in urine.

Cases 249 and 250 have been chosen to quantify delayed urinary excretion of Pu and the influence of pulmonary administration of DTPA compared with i.v. In fact, the increased urinary excretion of Pu on the first day after treatment corresponds only to 10 % of the cumulative urinary excretion associated with 1 DTPA administration. Half of the total urinary excretion of Pu-DTPA is achieved within

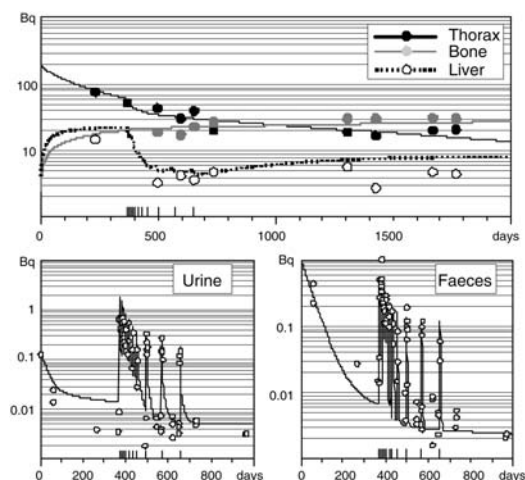


Figure 4. One of the best fit obtained for case 17 (Am type M/S). Each bar on the x-axis corresponds to a DTPA i.v.

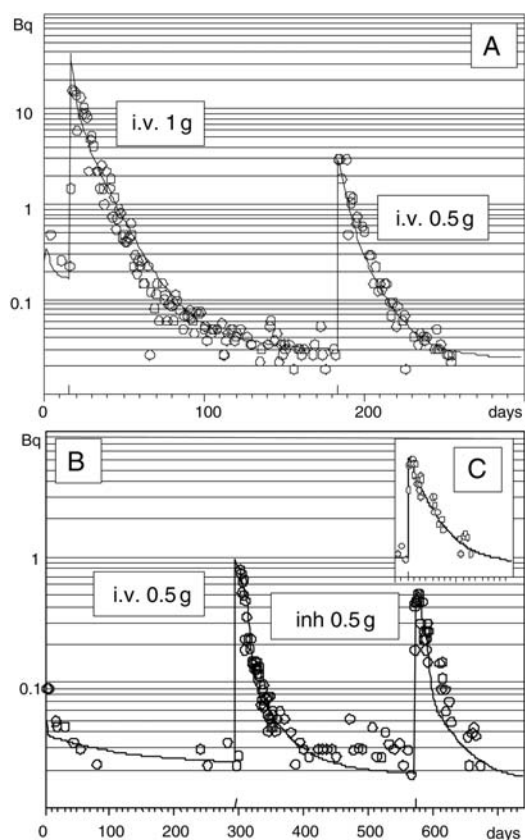


Figure 5. Urinary excretion of Pu after inhalation of the same radiocontaminant. A: case 249, B: case 250 and C: fit after DTPA inhalation taking into account an increased retention of free chelating agent in the lungs.

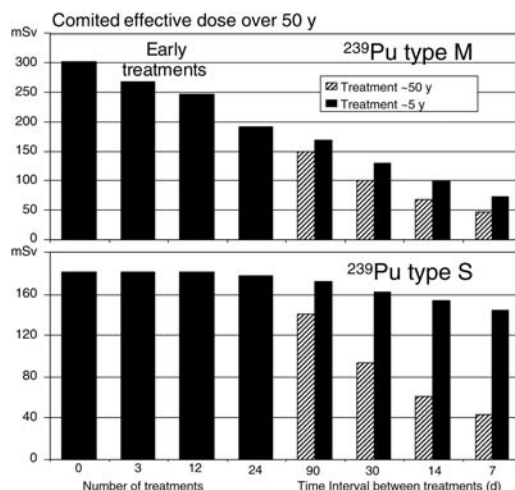


Figure 6. Simulations of effective dose reduction obtained after different DTPA treatment schedules following a 650 Bq wound by type M or S ^{239}Pu .

1 week, whereas 75 % within 2 weeks. Pulmonary administration of DTPA increases delayed excretion which is in agreement with a chelation of newly dissolved Pu. Good fit of this delayed excretion could be obtained by increasing the amount of free chelating agent retained in the lungs.

In these different cases, similar DTPA amounts were administered ($\sim 30 \mu\text{mol kg}^{-1}$). The fits shown in the figures were obtained by using similar ef values for both early chelation ($\text{ef}_b = \text{ef}_{\text{liver}} = 0.8$ and $\text{ef}_{\text{blood}} = 0.1$) and delayed chelation ($\text{ef} = 0.8$ in f_b and liver when free DTPA concentration was larger than the threshold).

Although good fits are obtained for most cases studied (more than 12), this does not mean that our modelling approach is validated. In fact, it is a pure fitting assessment and new experimental data are needed, especially as a concern range of some parameter values (f_b , s_b , ef_{liver} , ef_{blood} ...), so that realistic parameters could be applied to human. Moreover, intracellular chelation in soft tissues such as red bone marrow and gonads has to be considered for dosimetric benefits due to their high W_T values.

Simulations to improve dose reduction by DTPA

The calculation of dose reduction associated with DTPA therapy has been done for each case studied. A simulation tool has been developed to assess dose reduction depending on the treatment schedule. Recently, an early treatment schedule has been proposed which corresponds to daily i.v. of Ca-DTPA (0.5 g) for 3 d, three times a week for 3 weeks and

once a week for 3 months⁽¹⁶⁾. Figure 6 shows after wound contamination the effective dose reduction for type M or S ^{239}Pu , associated with such a schedule and the dose benefits if treatment is continued for 5 or 50 y at different time intervals.

Long-term treatments can reduce doses by factors from 3 to 6. However, repeated i.v. for several years appear unrealistic but oral administration of DTPA might be done⁽¹⁷⁾. After wound, equivalent dose delivered locally is not taken into account for effective dose calculation. This is not the case after inhalation and for type M, the maximal dose reduction should be 92 %, whereas only 42 % for type S. However, potential chelation of colloids as well as alteration of alpha dose distribution within the lungs due to DTPA administration could contribute to health benefits not associated with a significant dose reduction. The lung equivalent doses correspond to average values and the presence of hot spots appears to reduce the occurrence of lung tumours compared with more homogeneous alpha irradiation⁽¹⁸⁾. Thus, chelation of actinides retained as f_b which are homogeneously distributed within lung parenchyma⁽⁶⁾ might reduce risk for lung tumour induction, whereas particle aggregation within fibrotic scars should decrease dose delivered to target cells⁽¹⁸⁾.

CONCLUSION AND PERSPECTIVES

This study shows that a simple modelling approach could be applied for management of DTPA therapy based on equivalent and effective dose reduction. Three different versions of MADOR are being developed:

- V1 is dedicated to physicians and radioprotection. It is a didactic tool corresponding to improvement of the previous MEDOR software^(19, 20). Very fast access to calculation results will be obtained by using simplified models.
- V2 is an accurate calculation tool for an expertise purpose.
- V3 is software taking into account actinide speciation and localisation in rodents. If improvement of DTPA efficacy can be obtained, e.g. using different galenic forms, this tool will be transposed to human to obtain the best dosimetric estimates.

V1 and V2 should be fully validated by the end of 2012 using both human data and results of new targeted animal experiments.

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